REMARKS

Applicants respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow. Applicants thank the Examiner for reconsideration of the restriction requirement. The claims as amended herein are distinct from the antibody of DeJonge *et al.*, as noted by the Examiner on page 2 of the Office Action, in that the DeJonge *et al.* antibody does not bind human CD3.

In the specification, paragraphs have been amended on page 27.

Claims 1-16, 20-23, 30, 33 and 35-43 are presently pending. Claims 1, 3, 4, 21, 30, 37, 40 and 41 are currently being amended and claims 44 and 45 are added. Support for claims 44 and 45 is found on page 9, lines 7-25 of the specification.

This amendment adds or changes claims in this application. Amendments to the claims are not intended to limit the scope of the invention but are meant to clarify the invention. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

1. Objections to the Specification

Applicants have amended the specification to delete embedded hyperlink and/or other forms of browser-executable codes.

2. Rejections under 35 U.S.C. § 112, 2nd Paragraph

Claims 1-4, 21-23, 30, 33, 35-38 and 40-are rejected as indefinite for specification for the specific reasons set forth below.

2.1 Claims 1, 21 and 30

The Examiner alleges that claims 1, 21 and 30 are indefinite in the recitation of "a first domain comprising a binding-site of an immunoglobulin chain or an antibody." The Examiner alleges that this language is confusing because he does not know whether the

domain is from a binding site of an immunoglobulin or is the domain of an antibody or is an antigen binding region of an antibody.

Applicants respectfully traverse this rejection and submit that the language of these claims is scientifically clear to an immunologist, the skilled person in the art. The language of claims 1, 21 and 30 recites that the first and second domains comprise a binding-site that recognizes the CD19 antigen and the CD3 antigen, respectively. Applicants submit that the claim language make it clear to the skilled person that the binding sites are present in an antibody or in an immunoglobulin chain. Applicants have amended claims 1, 21 and 30 to revise the language slightly but applicants believe that the claim is definite as presently written. In view of these comments and minor claim amendments, it is requested that this rejection be withdrawn.

2.2 Claims 1, 21 and 30

The Examiner alleges that claims 1, 21 and 30 are indefinite in the recitation of "a single chain multi-functional polypeptide ... an antibody specifically recognizing the CD 19 antigen; and an antibody specifically recognizing the human CD3 antigen" because "it is unclear how a single-chain polypeptide can be an antibody or made up from an antibody because antibodies are made up of multiple chains of polypeptides not just one chain."

Again, applicants respectfully traverse this rejection because single-chain antibodies were known in the art and they are known to bind to antigens before the filing date of the present application. Single-chain antibodies are characterized in that they comprise the V_H and the V_L chain of an antibody on one peptide chain. Several single-chain antibodies are described in the literature (and cited by the Examiner in his Office Action; see, for example Mack, which has been analyzed and applied by the Examiner on page 8 of the Office Action against the pending claims). In regard to Mack, the Examiner's attention is directed to the sentence bridging the first and second column of page 7021, "[t]o overcome these problems, we have developed a procedure by which two single-chain Fv (sc-Fv) fragments (15,16) directed at the 17-1A antigen and the CD3 antigen on T lymphocytes were linked by ..." A review of the cited references 15 and 16 will show that these publications were published in 1988. Clearly, the Examiner's use of Mack to reject the pending claims should provide

sufficient evidence that the structure of a single-chain antibody is known and it is a recognized term in the art to skilled persons.

Additionally, applicants herewith provide further information that shows the Examiner the structure of single chain antibodies (Appendix 1). Applicants submit that the phrase that the Examiner has objected to is not indefinite, and it is requested that the Examiner reconsider his position on this issue.

2.3 Claims 3, 37 and 41

The Examiner states that the use of the word "mimic" is indefinite. Without acquiescing to the Examiner's position and in an effort to expedite prosecution, applicants have amended these claims to delete the term "mimic or" in these claims. It is requested that this rejection be withdrawn.

2.4 Claim 4

The Examiner states that the feature "said antibody" is indefinite because it lacks proper antecedent basis. Without acquiescing to the Examiner's position and in an effort to expedite prosecution, applicants have amended claim 4 so that it depends from claim 1. Claim 1 recites "an antibody..." and therefore, applicants submit that the term in claim 4 has proper antecedent basis in claim 1. It is requested that this rejection be withdrawn.

2.5 Claim 40

The Examiner states that claim 40 is indefinite as claim 20 recites a method in which the single chain antibody of claim 1 has only two domains. Applicants disagree with the Examiner's interpretation of claim 20 as claim 1 is open language that would allow the addition of another domain. Without acquiescing to the Examiner's position and in an effort to expedite prosecution, applicants have amended claim 40 to recite "... of claim 20, wherein the single-chain multifunctional polypeptide comprises at least one further domain". It is requested that this rejection be withdrawn.

3. Rejection under 35 U.S.C. § 112, first paragraph

Claim 11 is rejected as not being enabled for any single chain polypeptide that binds CD3 and CD19 which does not comprise an entire binding site of an antibody. On page 4 of the Office Action, the Examiner concedes that the specification is enabled for a single chain multi-functional polypeptide that binds CD19 and human CD3 wherein the binding domains of CD3 comprises six CDRs encoded by nucleotides 847 to 1203 and 1258 to 1575 of SEQ ID NO:9 or any other nucleotide that encodes six CDRs from a binding site of an antibody that binds CD3 and the CD 19 binding site comprises six CDRs and is encoded by a nucleic acid of 82 to 414 and 460 to 831 of SEQ ID NO:9 or a nucleic acid encoding a binding site of an antibody that binds CD19. Additionally, the specification discloses how to determine whether the single-chain multi-functional polypeptide binds to the target antigens, CD19 and CD3. See Example 3 beginning on page 34, where such binding is determined by FACS analysis. Thus, applicants submit that the specification discloses how a person skilled in the art can select polypeptides that bind to the target antigens using standard techniques that do not require undue experimentation.

Applicants' single-chain multi-functional polypeptide requires that the binding site in the first domain binds to the CD19 antigen and that the binding site in the second domain binds to the CD3 antigen. Claim 11 depends from claim 1 and possesses the binding characteristics of claim 1. The Examiner is referred to the specification beginning with the sentence bridging pages 2 and 3, where it is recited that the "invention may comprise at least one complementarity determining region (CDR) of an antibody or immunoglobulin chain recognizing the CD19 and CD3 antigens, respectively." Additionally, on page 9, lines 7 – 25, beginning specifically with line 11, it is recited that "at least one CDR, more preferred two, most preferred three CDRs of the VH and VL region" should be present in the polypeptide. As noted above, the specification provides a method to select for single-chain multi-functional polypeptides that contain a first and second domain with binding sites to CD19 and CD3 respectively. Therefore, applicants submit that claim 11 and new claim 44 are enabled by the specification.

In support of this position, applicants herewith provide two abstracts which support applicants' position that not all CDRs are necessary for an antibody to bind to its antigen. For example, in Olsen *et al.* (Appendix 2), the minimal structural elements necessary for

intracellular function were analyzed by selective deletion of CDR1 and CDR2. The results demonstrate that the variable heavy (VH)-CDR1 and CDR3 were shown to play a key role in antigen binding activity but that VH-CDR2 was "dispensible." The abstract by Sompuram *et al.* (Appendix 3) disclose the results of analysis of antigen binding and idiotypic expression by antibodies in which the CDRs were replaced by polyglycine. These abstracts support applicants' position that it is within the skill of the artisan to analyze antibodies and determine whether all six of the CDRs are necessary for an antibody molecule to bind to its antigen.

In view of the above arguments and claim amendments, it is requested that this rejection be withdrawn.

4. Rejection based on 35 U.S.C. § 103

Claims 1-16, 20-23, 30, 33 and 35-43 are rejected as being obvious over Bohlen *et al.* ("Bohlen"), and further in view of Mack *et al.* (PNAS 92:7021-7025, 1995) ("Mack") as evidenced by the specification and Blattler *et al.* ("Blattler").

The Examiner alleges that Bohlen teaches a bispecific antibody that binds CD19 and human CD3 and a method of preparing this antibody and a method of treatment with the antibody. However the Examiner concedes that Bohlen does not teach a single chain bispecific CD19 x human CD3 antibody or methods to treat non-Hodgkin's lymphoma with an antibody. The Examiner contends that Mack and Blattler make up these deficiencies. The Examiner cites Mack as disclosing a single chain bispecific antibody that binds CD3 and 17-1 methods of treatment with and method of making this single-chain antibody. The Examiner has applied Blattler as teaching that the CD19 antigen is expressed in all B-CLL and all non Hodgkin's lymphomas.

Thus the Examiner concludes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time that the invention was made to produce a single-chain bispecific antibody from the bispecific antibody of Bohlen by the method of Mack for the treatment of non-Hodgkin's lymphoma. The Examiner further alleges that one skilled in the art would have been motivated and had a reasonable expectation of success to have produced a single-chain bispecific antibody as set forth above because Bohlen teach that a bispecific binding agent which binds CD19 and human CD3 can be used for the treatment of B-CLL

and as taught by Blattler, the CD19 antigen is expressed in all B cell non-Hodgkin's lymphomas. Therefore, the Examiner further alleges that it would have been obvious to treat Non-Hodgkin's lymphoma with a bispecific molecule, a bispecific antibody directed to CD19 and CD3.

Applicants respectfully disagree with the Examiner's interpretation of the cited references and the basis for combining these references. In response, applicants wish to point out that the bispecific antibody against CD19 and CD3 described by Bohlen was produced by hybrid-hybridoma technology. The bispecific monoclonal antibodies were tested for functional activity in a cytotoxicity assay with LAZ-509 B cells as target (page 1807 left column). As shown in Fig. 2, cytotoxicity was measured in a 3h ^{51}Cr release assay using an E:T ratio of 10:1. In this Figure "antibody dilution" is shown without referring to the concentration of bispecific monoclonal antibodies needed to achieve half maximal lysis.

As clearly stated by the authors on page 1808 left column, T cell stimulation could **only** be achieved by **combination** of the bispecific antibody against CD19 and CD3 and a monospecific anti CD28 antibody. In Fig. 3B, it is shown that a reduction of CD19+ malignant B cells from 100% to about 78% was only achieved if the bispecific monoclonal antibody against CD19 and CD3 was combined with a bivalent monospecific anti CD28 antibody. The legend of Fig. 3 also describes that 100 ng/ml of bispecific monoclonal antibody against CD19 and CD3 were required to achieve this effect.

Further, as also shown in Table 3, cytotoxicity achieved with the bispecific monoclonal antibody against CD19 and CD3 ranged from 15% to 28% specific lysis at an E:T ratio of 10:1.

As the Examiner has stated, Bohlen does not teach a single chain bispecific CD19 X human CD3 antibody or methods of treating with such an antibody. But based on the teachings of Mack, the Examiner alleges that one skilled in the art would be motivated to make a single-chain bispecific antibody form Bohlen's bispecfic antibody using Mack's method.

Although the Examiner has tried to combine the teaching of Mack with the teaching of Bohlen to reject the pending claims, applicants submit that Mack describes the construction of a single-chain bispecific (scFv) anti-mouse EpCAMxanti-human CD3. Based on the disclosure in Mack with its scFV molecule, applicants submit that the results in Mack

do not motivate a skilled person in the art to produce a single chain bispecific antibody from Bohlen's bispecific antibody. As shown in Fig. 5 of Mack, this scFv molecule has a half maximal cytotoxic activity on Kato cells at a concentration of 1.6 ng/ml. On EpCAM expressing HT-29 cells, a half maximal cytotoxic activity was achieved with 40 ng/ml. E:T ratios of 20:1 were required for specific lysis of target cells. As shown by Mack, a concentration of scFv of about 20 ng/ml is necessary to induce half maximal lysis at an E:T ratio of 4:1. Therefore, following from these data, one skilled in the art would **not** be motivated to produce and use a single-chain specific antibody for treatment. Particularly, in view of the unexpected properties that the scFv anti-human CD19 X anti-human CD3 of the present invention has:

- an 10-100x increased half maximal cytotoxic activity of 0.1 ng/ml (E:T = 20:1).
- has the same high bioactivity at low E:T ratios of 5:1 (half maximal cytotoxic activity at 0.1 ng/ml) and even 2.5:1 (half maximal cytotoxic activity at 0.1 - 1 ng/ml) as shown in Example 4, page 35 and Fig. 7 of the present invention.

In regard to the application of Blattler, this cited reference does not render the present invention obvious and does not cure the deficiencies of Bohlen and Mack. Blattler discloses immunoconjugates of a monoclonal anti CD19 antibody and lectins and the use of these conjugates for treatment of medical conditions adversely associated with B cells expressing the CD19 antigen (column 38, line 43 to 45). As described by Blattler, full immunoglobulins were used for conjugation with lectins inducing killing of CD19+ target cells. Blattler did not describe bispecific antibodies or single chain constructs modulating the cellular immune response *in vivo*.

Applicants submit that from the teachings in Bohlen, Mack and Blattler, it could not be expected from a person skilled in the art that a single-chain bispecific antibody against CD19 and CD3 **alone** leads to sufficient T cell activation and as a consequence reduction of the number of CD19+ target cells. Since concentrations of 100 ng/ml of the bispecific antibody were required, it could not be expected from a person skilled in the art that a bispecific monoclonal antibody shows biological activity at a concentration of 0.1 to 1 ng/ml as observed for the construct of the present invention.

Even if a person skilled in the art would have combined Mack and Bohlen, he/she would have expected that the optimal biological activity of a bispecific antibody against CD19 and CD3:

- is only obtained in combination with an anti CD28 antibody
- requires concentrations from 20 to 100 ng/ml
- requires high E:T ratios.

Accordingly, and in contrast to the allegations set forth by the Examiner, one of ordinary skill in the art was certainly not motivated and did not have a reasonable expectation of success in producing the single chain bispecific antibody molecule as claimed. In particular, the construct of the present invention has proven to be clinically very active and to comprise a very high bioactivity as documented in the application as filed as well as explained herein above. In view of the above arguments, it is requested that this rejection be withdrawn

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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